AMERICAN SOCIETY FOR MICROBIOLOGY

Journal of Virology®

The 13th International Double-Stranded RNA Virus Symposium, Houffalize, Belgium, 24 to 28 September 2018

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ABSTRACT The triennial International Double-Stranded RNA Virus Symposium, this year organized by J. Matthijnssens, J. S. L. Parker, P. Danthi, and P. Van Damme in Belgium, gathered over 200 scientists to discuss novel observations and hypotheses in the field. The keynote lecture on functional interactions of bacteria and viruses in the gut microbiome was presented by Julie Pfeiffer. Workshops were held on viral diversity, molecular epidemiology, molecular virology, immunity and pathogenesis, virus structure, the viral use and abuse of cellular pathways, and applied double-stranded RNA (dsRNA) virology. The establishment of a plasmid only-based reverse genetics system for rotaviruses by several Japanese research groups in 2017 has now been reproduced by various other research groups and was discussed in detail. The visualization of dsRNA virus replication steps in living cells received much attention. Mechanisms of the cellular innate immune response to virus infection and of viral pathogenesis were explored. Knowledge of the gut microbiome's influence on specific immune responses has increased rapidly, also due to the availability of relevant animal models of virus infection. The method of cryo-electron microscopic (cryo-EM) tomography has elucidated various asymmetric structures in viral particles. The use of orthoreoviruses for oncolytic virotherapy was critically assessed. The application of llama-derived single chain nanobodies for passive immunotherapy was considered attractive. In a satellite symposium the introduction, impact and further developments of rotavirus vaccines were reviewed. The Jean Cohen Lecturer of this meeting was Harry B. Greenberg, who presented aspects of his research on rotaviruses over a period of more than 40 years. He was also interviewed at the meeting by Vincent Racaniello for the 513th session of *This Week in Virology*.

KEYWORDS double-stranded RNA virus

The 13th International Double-Stranded RNA Virus Symposium took place in Houffalize, Belgium, at the convention center Vayamundo, from 24 to 28 September 2018. The first of these meetings was held in St. Thomas, VI, USA, in 1982, and they have reconvened triennially ever since. The meeting in the surroundings of the beautiful autumnal Belgian Ardennes mountains was very ably organized by Jelle Matthijnssens (KU Leuven, Belgium), John S. L. Parker (Cornell University, USA), Pranav Danthi (Indiana University, USA), and Pierre Van Damme (University of Antwerp, Belgium), and the scientific proceedings were complemented by attractive social activities and a festive dinner with dancing at the Château Jemeppe. The meeting was generously sponsored by national and international donors, allowing the organizers to issue 44 full grants, 39 travel grants, and 11 NIH grants to young researchers. Over 220 scientists and health professionals from 42 countries on five continents attended.

The keynote lecture, "How Transkingdom Interactions Influence Viral Infection," was presented by Julie Pfeiffer (University of Texas Southwestern Medical Center). Enteric viruses interact with other components of the gut microbiome in various ways (1), with consequences for pathogenicity. In addition, complexes of certain bacteria with viruses

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and viruses shed in vesicles can lead to a high-multiplicity infections of individual cells, resulting in gene reassortment of segmented RNA viruses and genome recombination of positive-sense single-stranded RNA viruses [ss(+)RNA viruses]. Consequences of these findings for viral evolution and fitness are just beginning to be explored (2).

Oral presentations were in workshops on viral diversity, evolution and epidemiology, molecular and cellular virology, immunity and pathogenesis, viral structures, the use and abuse of viral pathways, applied double-stranded RNA (dsRNA) virology, and rotavirus vaccines (as a satellite workshop). Besides the 100 oral presentations (including 43 short "shotgun" presentations), many data were displayed in approximately 164 posters, with some of them being communicated as shotgun presentations in the oral sessions. Two 2-h sessions were dedicated to study and discussion of the posters.

It is a daunting task to do justice to all the work presented at the symposium. For more detailed information, the Abstract Book of the meeting is available as a .pdf file at https://kuleuvencongres.be/dsRNA2018/. The work reviewed in the following has particularly impressed the author of this report.

Viral diversity. Nobuhiro Suzuki (Okayama University) reported on a novel interaction of a capsidless ss(+)RNA virus with a dsRNA virus, coinfecting a phytopathogenic fungus. The ssRNA is *trans*-encapsidated by the capsid protein of the dsRNA virus, together with the RNA-dependent RNA polymerase (RdRp) of the dsRNA virus, and replicated as if it were a dsRNA virus (3), with interesting taxonomic and evolutionary considerations (4).

Souvik Ghosh (Ross University) reported on a high degree of diversity of the gene segments 2 (encoding the RdRp) of picobirnaviruses isolated from a variety of mammalian host species (5).

Marylin J. Roossinck (Penn State University) drew attention to the remarkable difference in the degree of variation of dsRNA viruses isolated from various plants and fungi (mostly *Partitiviridae*), with their RdRps being highly conserved (monophyletic), suggesting cross-kingdom transmissions, and their coat proteins being highly variable (polyphyletic) and, thus, probably co-opted from various different sources (6).

Houssam Attoui (INRA, Ecole Nationale Vétérinaire d'Alfort) presented the proposal of elevating the family *Reoviridae* to the order *Reovirales*, in which the previous subfamilies become the families *Sedoreoviridae* and *Spinareoviridae*. While the RdRps of the *Birnaviridae* are relatively closely related to those of the *Spinareovirinae*, there are structural arguments against including the *Birnaviridae* in the new order.

The proposal was explored further in a round table discussion. There was agreement that classification by sequence data was very important (7) but that a minimum amount of sequence and/or additional data would have to be available. Challenges in the difficulties of classification of reassortants of segmented RNA viruses, of marine bacteriophages, and of endogenous retroviral sequences were raised.

Evolution and epidemiology. Kristen Ogden (Vanderbilt University Medical Center) analyzed numerous G12P[8] species A rotaviruses (RVAs) isolated in Nashville, TN, from 2011 to 2013. There was evidence of multiple separate introductions of these strains into the defined geographical area where RVA universal mass vaccination (UMV) had been introduced several years ago. Whether emergence of these viruses is due to immune pressure exerted by RVA vaccine strains is not clear at present (8).

Tohru Suzuki (National Institute of Animal Health) analyzed species H rotavirus (RVH) isolates from pigs and observed NSP3 genes of different lengths in several isolates, some of which were possibly derived from recombination events with species C rotavirus strains.

Francis K. Shepherd (University of Minnesota College of Veterinary Medicine) noted hypervariability in particular sites of the VP7 genes of pig RVAs, which, however, only partially overlapped with known neutralization epitopes. The VP7 and VP4 genes of the porcine RVAs were markedly different from those of a commercial RVA swine vaccine.

Celeste M. Donato (Monash University) reported on RVA surveillance in Australia after the introduction of RVA vaccines. (Some states used Rotarix, some RotaTeq.) While

both vaccines were effective, the diversity of genotypes of RVA isolates had increased in different directions in different states and was suggested to possibly be due to different immunological pressures by vaccine strains.

Filemon Bucardo (National Autonomous University of Leon) noted a possible dependence of RVA vaccine strain shedding and the histo-blood group antigen (HBGA) secretor status of vaccinated children.

Leen Beller and Ward Deboutte (Laboratory of Viral Metagenomics of KU Leuven) explored the viromes of infants and of honeybees, respectively, and found a wide diversity of different viral genomes, some of them representing novel clades.

Chantal A. Agbemabiese (University of Ghana) analyzed multiple RVA genome sequences of DS-1-like genotype constellation 2 and proposed a system, permitting classification at the subgenotype level, based on differences in phylogenetic lineages/clusters. While desirable, the method will require further refinement.

After the introduction of RVA UMV in Burkina Faso, Johan Nordgren (Linkoeping University) observed that acute gastroenteritis (AGE) in most children in 2015 was associated with norovirus (NoV) infections of diverse genotypes.

Susan Damanka (University of Ghana) reported the observation that several Ghanaian RVA P[8] strains were untypeable since the strains had mutated in the VP8* region where the primers for the reverse transcription-PCR (RT-PCR) method used for typing did not bind anymore; this phenomenon also had occurred with VP7 genes of RVA G2 strains (9).

Tina Mikuletič (University of Ljubljana) discovered all 3 orthoreovirus serotypes and various reassortants thereof in Slowenian bat populations (10) and showed that bat orthoreoviruses can spread systemically in newborn mice.

Molecular and cellular virology. Takeshi Kobayashi (Osaka University) reviewed the development of reverse genetics (RG) systems in the *Reoviridae* family. While helper virus-free systems have been available for some time for members of the genera *Orthoreovirus* (11–13) and *Orbivirus* (14–17), for RVAs this became possible in 2017 due to procedural refinements (18, 19). The breakthrough occurred by cotransfection of transcription plasmids encoding the 11 full-length RVA segments in combination with expression plasmids producing capping enzyme (since cDNA transcripts inside the cell are not capped) and a virus-encoded, fusion-active small transmembrane (FAST) protein (20). The rescued virus could be further manipulated by fusing heterologous genes (e.g., encoding fluorescence proteins) to the gene of one of the segments; cells infected with such recombinant virus fluoresce, and the recombinants can be used for testing of antivirals *in vitro* and for live-cell imaging (18). An alternative procedure did not require the expression of FAST protein, but the relative concentrations of transfected transcription plasmids encoding NSP2 and NSP5 were increased 3-fold (19). RVA RG systems are now functioning in >10 laboratories worldwide (with several presentations shown at the meeting), and further refinements and various applications of the system will permit still-impossible explorations of RVA replication, pathogenesis, and other complex host factors in the years to come.

Asha A. Philip (Indiana University) has applied RVA RG to express a Japanese eel fluorescence protein (Unagi) from a RVA segment fusion gene, using expression of the capping enzyme of African swine fever virus as a cofactor (21). Yuta Kanai (Osaka University) used RVA RG to produce SA11 virus reassortants carrying the VP7 and VP4 genes of human RVAs, including those genes obtained from fresh clinical isolates.

RVA RG was further explored in a lively evening session attended by many meeting participants. Takeshi Kobayashi and John Patton reported on their practical experience with RVA RG. It was revealed that the small details of the procedures are very important, such as the cell lines used and their maintenance, the transfection reagents, the FAST proteins, the starting plasmid used for insertion of RVA full-length cDNAs, the constitutional expression of T7 polymerase in cell lines, etc. It was agreed that the researchers who had gained experience with the new system will draft protocols, exchange and comment on them, and make advanced or final versions available to the scientific

community. There was excitement that the new system will permit many experiments which so far have not been possible and that the future of RVA (and non-RVA RV) RG looks extremely bright.

Pursuing long-standing work with reoviruses by the Boulant laboratory, Marta Fratini (Heidelberg University and Deutsches Krebsforschungszentrum) explored the physical parameters of early virus-host cell interaction by immobilizing reovirus particles and nanoparticles of different sizes on surfaces to study the formation of clathrin-coated vesicles (CCV) in interacting cells. It was found that CCV formation is independent of cargo size; the forces needed to form the CCV curvature were measured by molecular tension force microscopy (22, 23).

Bernardo Mainou (Emory University) linked chemotherapeutic agents to reovirus particles to increase the toxicity to tumor cells and minimize off-target effects of anticancer treatments (24).

Durga Rao Chilakalapudi (Indian Institute of Science) presented data indicating that RV viroplasms interact with various proteins of stress granules and P bodies which are inhibited or disrupted in the course of the viral infection (25).

Po-yu Sung (London School of Hygiene and Tropical Medicine) had investigated the interaction of the bluetongue virus VP6 with various viral RNA segments, using combinations of biochemical, in vitro particle reconstitution, and RG procedures. VP6 sequences were identified which are involved in RNA interaction; there is ongoing work to establish a full picture of viral RNA assortment and packaging mechanisms.

Peter van Rijn (Wageningen Bioveterinary Research) reviewed orbivirus research which has progressed rapidly, due to the development of RG systems for orbiviruses of major importance for animal health (see above). He drew attention to the ability to rescue "synthetic reassortants" (i.e., not found in nature) and to the production of novel vaccine candidates such as disabled infectious single cycle (DISC) strains (26, 27) and disabled infectious single animal (DISA) strains (28).

Catherine Eichwald (University of Zürich) explored the interaction of RVA NSP5 and the core protein VP2, which form viroplasm-like structures (VLS) when coexpressed in uninfected cells. Particular amino acids of VP2 needed for interaction with NSP5 which were also required for triggering NSP5 hyperphosphorylation were identified. Although the in vivo function of NSP5-VP2 interaction is not clear at present, the binding region may lend itself to the development of anti-RVA antivirals.

Eric Salgado (Harvard Medical School) followed up on the tracking of fluorescently labeled reconstituted RVA triple-layered particles (rcTLPs) during entry into living cells by labeling rcTLPs with a Ca^{2+} sensor, rhodamine 5F azide, and observing the infection pathway. It was found that Ca^{2+} loss starts 2 min before the loss of VP7 and 7 min before DLP release (29, 30).

Joseph Hyser (Baylor College of Medicine) characterized the RVA-induced Ca^{2+} signaling dynamics by infecting human enteroids engineered to stably express the calcium indicator GCaMP (a fusion product of green fluorescent protein, calmodulin, and M13, a peptide of the myosin light chain kinase). RVA infection increased Ca^{2+} signaling and generated intercellular calcium waves the visual presentation of which was very impressive; this could be prevented by purinergic inhibitors. The paracrine signaling pathway is considered to be critical for various factors of RVA pathogenesis.

Oscar Burrone (International Centre for Genetic Engineering and Biotechnology) reported on the anti-RV activity of compound ML-60218, a mammalian RNA polymerase III inhibitor. ML-60218 was found to disrupt viroplasms, inhibit the production of infectious viral progeny, and also damage the outer structure of VP6, thus destabilizing dual-layered particles (DLPs) (31).

Sue Ellen Crawford (Baylor College of Medicine) conveyed the observation that NSP2 in RVA-infected cells interacts with DGAT1, a neutral lipid synthase, leading to DGAT1 degradation and to an increase of RVA infectious progeny, suggesting that precursor lipids are redirected into phospholipid production required for viroplasm/lipid droplet interaction (32).

Wico Sander (University of the Free State) showed that supplementation of RVA-infected cells with unsaturated fatty acids (e.g., oleic acid) increased the yield of infectious viral progeny significantly, whereas supplementation with saturated fatty acids had no such effect.

Adrish Sen (Stanford University) updated findings that RVA-infected cells develop strong STAT-1-mediated immune responses which are counteracted by the viral NSP1 and the degradation of interferon (IFN) receptors (33).

Eiko Matsuo (Kobe University) developed a RG system for Ibaraki virus, a member of the *Orbivirus* genus, and succeeded in producing replication-competent viruses which carry a fluorescently labeled VP6 in their core (16).

Immunity and pathogenesis. Cathy Miller (Iowa State University) reviewed work on the interaction of mammalian orthoreovirus (MRV) proteins with stress granules (SGs) which arise in cells after MRV infection but then disappear, due to the interaction of the SG protein G3BP1 with the MRV protein sigmaNS. Since SGs contain the RACK protein, which regulates HIF-1, a master transcriptional activator in tumor cells, MRV infection may in this way act as an oncolytic agent (34, 35).

Karl Boehme (University of Arkansas for Medical Sciences) explored the mechanism of action of the MRV sigma1s protein, using sigma1s-null MRV and IFNAR1$^{-/-}$ cells, and concluded that sigma1s promotes viral spread to cells in the presence of a functional IFN-1 response (36).

Marie Hagbom (Linkoeping University) investigated the role of enteric glial cells (EGCs) in RVA infection; EGCs are stimulated by serotonin and contribute to the maintenance of tight junctions in enteric epithelia.

Bluetongue virus (BTV) causes symptomatic infections mostly in sheep but not in cattle. Using an expression library of IFN-stimulated genes in bovine cells, Alexandra Hardy (MRC-University of Glasgow Centre for Virus Research) identified 10 genes which interfere with BTV replication and is in the process of investigating the sheep orthologues for anti-BTV activity.

Siyuan Ding (Stanford University) reported work on RVA-host cell interactions. SAMD9, already known as a cellular restriction factor of other viruses, was identified as a potent host restriction factor of RV replication; however, it is also targeted by RVA NSP1 for degradation. RVA infection was found to induce host cell DNA damage, and genetic deletion of components of the DNA sensing pathway increased RV replication *in vitro* and *in vivo* (37).

Lyndsay Cooke (Pirbright Institute) presented the interesting observation that in the presence of *Culicoides* (the insect vector's) saliva BTV replication in bovine monocytes is increased and that this is likely due to the presence of bacterial lipopolysaccharides, which may alter cell entry mechanisms.

Gwen Taylor (University of Pittsburgh) reported that mice lacking NF-κB p65 expression in neurons (established by the Cre/loxP recombination system) mostly survived MRV infection, in contrast to MRV-infected wild-type mice, suggesting that NF-κB-dependent factors are mediators of neuropathogenesis.

Vanessa Harris (Amsterdam Institute for Global Health and Development) compared the intestinal microbiome of RVA vaccine responders and nonresponders in rural Ghana and fond that vaccine responsiveness is correlated with a diminuished abundance of *Bacteroidetes* spp. and an expansion of *Gammaproteobacteria*; the presence of members of the *Picornaviridae* correlated with nonresponsiveness. The molecular mechanisms of the "transkingdom" microbiome affecting vaccine responses remain to be studied further (38–41).

Sarah Caddy (MRC-Laboratory of Molecular Biology) investigated the function of RVA VP6-specific antibodies as potential correlate of protection by electroporating various RVA-specific monoclonal antibodies into cells, an assay by which intracellular neutralization (ice NT) could be tested. She found good correlation of ice NT titers with degrees of inhibition of ss(+)RNA transcription *in vitro*.

Linda Saif (Ohio State University) showed in a gnotobiotic piglet model that malnutrition was associated with a decrease in immune response to human RVA vaccine and correlated with a lower protection rate after challenge, even if transplanted with human infant fecal microbiota (42).

Viral structures. Yizhi Tao (Rice University) reported that coexpression of a human picobirnavirus (hPBV) RdRp with the cognate capsid protein (CP) resulted in the synthesis of virus-like particles (VLPs); VLPs of hPBV and rabbit PBV were very similar in structure and had conserved glycan binding motifs (43).

Using superresolution microscopy, Yasel Garcés Suarez (Autonomous National University of Mexico) reported on the content of RVA-induced viroplasms: viral NSP5 was found at the center, surrounded by concentric rings of NSP2, NSP4, VP1, VP2, and VP6 (in that order).

Alexander Borodavka (Universities of Leeds and Munich) presented biophysical data on assortment mechanisms of RVA RNA segments *in vitro*: their interaction with NSP2 leads to conformational RNA rearrangements, permitting specific RNA-RNA contacts. The findings await probing by reverse genetics experiments (44).

Liya Hu (Baylor College of Medicine) reported glycan array, crystallographic, and cell culture studies aimed at exploring the structural basis of glycan binding sites of RVAs, which are highly variable and may explain neonate and host specificities and other complex biological activities (45).

Dilip Kumar (Baylor College of Medicine) expressed and purified RVA VP3 and determined its structure from cryo-electron microscopic (cryo-EM) data at a resolution of 3.2 Å. The purified protein showed high affinity binding to ssRNA and exhibited the different activities of capping enzyme, which could also be located in atomic detail in different domains of the structure.

Adeline Kerviel (London School of Hygiene and Tropical Medicine), in collaboration with the group of Z. Hong Zhou (University of California Los Angeles [UCLA]), reported the atomic structure of the BTV NS1 protein, involved in upregulating viral protein translation. The structure analyzed consisted of tubules with 40 protomers per turn. Zinc finger motifs turned out to be critical for the NS1 function.

Z. Hong Zhou (UCLA) described the structure of dsRNA and attached transcriptional enzyme complexes (TEC) inside the cores of cytoplasmic polyhedrosis virus, a member of the *Cypovirus* genus of the *Reoviridae*. It was possible to visualize differences of TECs in the quiescent and transcriptionally active stages (46, 47).

Courtney Steger (Virginia Tech) identified amino acids at the surface of RVA VP1, the RdRp, which appeared to interfere with *in vitro* transcription in the presence of VP2, possibly due to loss of contact with VP2.

José Castón (Centro Nacional de Biotecnología) described the structures of capsid proteins of the cores of fungal dsRNA viruses, which can also interact with defective interfering RNAs, satellite virus RNAs, or other heterologous RNAs (48, 49).

Pranav Danthi (Indiana University) demonstrated that mixtures of two types of orthoreovirus (T1L and T3D), following incubation at 37°C, form aggregates and that infection with aggregates leads to a significantly higher reassortment rate than infection with mixed, nonaggregated viruses.

Using and abusing host pathways. Roy Duncan (Dalhousie University) reviewed the structure and functions of FAST proteins, encoded by aquareoviruses and orthoreoviruses, which convert cell-to-cell attachment into fusion synapses and have gained recent prominence as components of RV reverse genetics systems (18, 20). FAST proteins can also act as drug delivery platforms and enhance oncolytic virotherapy (50).

Michelle Arnold (Louisiana State University-Shreveport) described different mechanisms by which RV NSP1 prevents interferon (IFN) induction in RVA-infected cells by inducing degradation of IFN regulatory factors (IRFs) or of the NF-κB activator, beta-transducin repeat-containing protein (beta-TrCP) (51).

John Patton (National Institutes of Health and Indiana University) showed that a modified IkB-like phosphodegron in NSP1 is involved in the induction of beta-TrCP degradation in RVA-infected cells (52).

Terry Dermody (University of Pittsburgh) described how the cellular chaperonin TRiC is instrumental in proper folding of the orthoreovirus outer capsid protein sigma 3 for binding to protein mu1, forming stable heterohexamers (53).

Pavithra Aravamudhan (University of Pittsburgh) demonstrated neuronal migration of fluorescently labeled orthoreovirus particles following macropinocytosis, which can be inhibited.

Anupam Mukherjee (National Institute of Cholera and Enteric Diseases) contributed to the topic of cellular microRNAs (miRNAs) affecting viral replication by showing that RVA infection dysregulated various miRNAs leading to autophagy (54).

Jeanette Criglar (Baylor College of Medicine) investigated correlations of the interaction of RVA NSP2 and NSP5 with different phosphorylation steps of NSP5 in which the cellular kinase CK1alpha is involved and which control viroplasm assembly. Phosphorylation of NSP2 by CK1alpha appears to be an intermediate step (55).

Applied dsRNA virology. Don Morris (University of Calgary), an oncologist, spoke of his experience with using mammalian reoviruses as oncolytic agents. Working with murine tumor models, he found that reovirus application significantly reduced tumor burden, but he concluded that in humans oncolytic viruses were most effective in combination with various cytostatic agents (56).

Viviana Parreño (Instituto Nacional de Tecnología Agropecuaria) reviewed the work of her group on passive immune strategies to control enteric virus infections. RVA-specific IgY antibodies produced in egg yolk proved to be efficient for treatment of neonatal calf diarrhea. Her group also developed RVA VP6-specific llama-derived nanobodies (VHH) which are highly cross-reactive within RVAs and partially protective in suckling mouse and gnotobiotic piglet models. The RVA-specific VHH antibodies are at present being tested as candidate drugs to treat RVA AGE in infants (57–59).

Celina Guadalupe Vega (Instituto Nacional de Tecnología Agropecuaria) presented data on a cow transgenic for the production of RVA VP6-specific VHH antibodies and also on a diagnostic kit (Rotadial) in which VP6-specific VHH antibodies are used.

Based on her long-standing work with bacteriophage phi6, a trisegmented dsRNA virus, Minna Poranen (University of Helsinki) used phi6 RdRp and other components of the system to produce short dsRNA molecules which showed inhibitory activity in virus-infected plants and herpes simplex virus-infected skin when topically applied (60, 61).

Jana Van Dycke (University of Leuven) reported on a nucleoside viral polymerase inhibitor (7-deaza-2′-C-methyl adenosine) which interferes the replication of rotaviruses, noroviruses, and sapoviruses (62).

Maya Shmulevitz (University of Alberta) identified mutations in T3 reovirus enabling increased replication in tumor compared to nontransformed cells. The mutations were mainly located in the l1 and s1 (cell attachment) proteins (63).

Rotavirus satellite symposium. The rotavirus satellite symposium was devoted to reviewing the development, introduction, and impact of various RVA vaccines over a period of more than a decade. In >100 countries RV vaccination has become part of childhood Expanded Programs on Immunization (EPI) and has universally led to a decline of morbidity (severe acute gastroenteritis) and RV-associated mortality, although vaccine effectiveness is decreased in low- and middle-income compared to high-income countries (64, 65). B. Benninghoff (GSK) and Esmée de Wolde (Merck) produced updates on the Rotarix and RotaTeq vaccines, respectively (64, 66). Mithu Raychaudhuri (Bharat Biotech International) described the introduction of Rotavac in India in 2016 (67). Using CRISPR/Cas 9 methodology, Houping Wang (Centers for Disease Control and Prevention) described the production of Vero cells in which the WDR62 gene was knocked out and which permitted propagation of RVA vaccine strains to higher titers; the technology will require further exploration before it can be used for

vaccine manufacturing (68). The development of new candidate RVA vaccines was reviewed by Carl Kirkwood (Bill and Melinda Gates Foundation) (69).

Student classes. As an innovation, classes were offered before the start of the meeting for young scientists or researchers who joined the field recently. Lectures were provided on the following:

- dsRNA virus overview, by John S. L. Parker (Cornell University)
- Structure and entry, by Pranav Danthi (Indiana University-Bloomington)
- RNA synthesis mechanisms of dsRNA viruses, by Sarah McDonald (Wake Forest University)
- Immunology, by Michelle Arnold (Lousiana State University-Shreveport)

Jean Cohen Lecture. Since 2005 the International dsRNA Virus Symposia has celebrated the work of Jean Cohen (1943 to 2004; INRA and CNRS, France) through a lecture given in his honor. This meeting's Jean Cohen Lecturer was Harry B. Greenberg (Stanford University), who reminisced on his career, which, besides many other activities, spans >40 years of RVA research. He explored growth of human RVAs *in vitro*, analyzed details of the innate and acquired immune responses to RVA infection, identified viral and cellular factors determining host specificity, took a special interest in defining correlates of protection after RVA infection or vaccination, and was involved in the development of several RVA vaccines, most recently in India. Brilliant work identified B cells in the human gut submucosa producing antibodies which are broadly cross-reactive with and cross-neutralizing several genotypes/serotypes of human RVAs (70); this observation may be very important for the development of future RVA vaccine candidates.

This Week in Virology. Harry Greenberg's career and achievements were also explored in an interview, which Vincent Racaniello (Columbia University) had agreed to stage at this meeting, representing the 513th session of *This Week in Virology* (available at http://www.microbe.tv/twiv/). Besides the different stages of Harry's professional life, his involvement in work on RVAs, NoVs, astroviruses, hepatitis B virus, and influenza viruses was discussed.

Vincent Racaniello's endeavor to bring details of scientific thinking and achievements to the attention of the wider public was recognized by Jelle Matthijnssens, who, in the name of the meeting participants, presented an intaglio print to Vincent, in which different structures of viral particles were combined. (The image of this artwork can be seen on the Internet with the announcement of *This Week in Virology* no. 515.)

Site of 14th International dsRNA Virus Symposium. In a general meeting, the location of the 14th International dsRNA Virus Symposium (2021) was discussed, and the offer of Viviana Parreño to host it in Argentina was accepted.

ACKNOWLEDGMENTS

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